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The study of the diuretic activity and pharmacotechnological properties of a dry extract of *Salvia sclarea* L. growing in Tajikistan

Aim. To study the pharmacological activity of a dry extract of clary sage (DECS) growing in Tajikistan and its pharmacotechnological properties as basic stages in the development of the composition and technology of hard gelatin capsules with its content.

Materials and methods. For the studies, we used DECS standardized by the content of the total amount of flavonoids and hydroxycinnamic acids. The quantitative content of the total amount of flavonoids was not less than 13.0 % calculated with reference to apigenin, and the quantitative content of the total amount of hydroxycinnamic acids was not less than 1.2 % calculated with reference to rosmarinic acid. The pharmacotechnological properties of DECS were studied according to methods of the State Pharmacopoeia of Ukraine (SPhU).

Results and discussion. During screening, all doses of DECS studied showed a moderate diuretic activity. Thus, when using DECS in the dose of 100 mg/kg, the relative volume of the urine excreted by rats for 5 hours increased by 1.9 times, in the dose of 200 mg/kg – by 2.0 times, in the dose of 300 mg/kg – by 1.8 times compared to the same indicator in the negative control group ($p<0.05$). When studying the complex of pharmacotechnological properties, it was found that DECS was a finely dispersed amorphous powder with particles of isodiametric form. DECS had an average bulk weight of 0.515 ± 0.002 g/mL, and the fluidity assessment showed that DECS had a very poor flowability, which value in the vibration mode of the device was 2.8 ± 0.1 g/s. According to the study of the fractional composition, DECS had a clearly expressed fine fraction with a particle size of less than 0.25-0.09 mm 84.68 %.

Conclusions. Taking into account the results of the study of the diuretic activity and scientific literature data on the spectrum of the pharmacological activity of *Salvia sclarea* L, it is rational to consider DECS as a potential combined agent for enhancing the diuretic effect or in diseases of the urinary system accompanied by edema and inflammatory processes. The study of the pharmacotechnological indicators of DECS allows predicting the need to use certain groups of excipients to develop the composition and technology of capsules with its content, namely antifriction substances to improve fluidity and disintegrants to improve capsule disintegration, as well as substances that contribute to the compaction of bulk mass and moisture-regulating agents.

Keywords: *clary sage (Salvia sclarea L.); dry extract; diuretic activity; pharmacotechnological properties; technology of solid dosage forms, hard gelatin capsules*

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Вивчення діуретичної активності та фармакотехнологічних властивостей сухого екстракту Salvia sclarea L., вирощуваної в Таджикистані

Метою дослідження було вивчити фармакологічну активність сухого екстракту шавлії мускатної (СЕШМ), вирощуваної в Таджикистані, та його фармакотехнологічні властивості як базові етапи розробки складу та технології твердих желатинових капсул з його вмістом.

Матеріали та методи. Для дослідження використовували СЕШМ, стандартизований за вмістом суми флавоноїдів та гідроксикоричних кислот. Кількісний вміст суми флавоноїдів становив 13,0 % у перерахунку на апігенін, а кількісний вміст суми гідроксикоричних кислот – 1,2 % у перерахунку на розмаринову кислоту. Фармакотехнологічні властивості СЕШМ вивчали згідно з методиками ДФУ.

Результати та їх обговорення. Під час проведення скринінгу всі досліджувані дози СЕШМ виявили помірну діуретичну активність. Так, за використання СЕШМ у дозі 100 мг/кг відносний об'єм виділеної сечі щурів за 5 годин збільшувався у 1,9 раза, у дозі 200 мг/кг – у 2,0 раза, у дозі 300 мг/кг – у 1,8 раза, якщо порівнювати з аналогічним показником у групі негативного контролю (р 0,05). Вивчаючи комплекс фармакотехнологічних властивостей, визначили, що СЕШМ є дрібнодисперсний аморфний порошок з частинками ізодіаметричної форми. СЕШМ має середню насипну масу 0,515 ± 0,002 г/мл, дуже погану плинність, значення якої в режимі вібрації приладу становить 2,8 ± 0,1 г/с. За даними вивчення фракційного складу, СЕШМ має чітко виражену дрібнодисперсну фракцію з розміром частинок менше 0,25-0,09 мм 84,68 %.

Висновки. З огляду на отримані результати вивчення діуретичної активності та даних наукової літератури щодо спектра фармакологічної активності *Salvia sclarea* L. раціонально розглядати СЕШМ як потенційний комбінований засіб для посилення діуретичної дії в разі захворювань сечовидільної системи, що супроводжуються

набряками та запальними процесами. Вивчення фармакотехнологічних показників СЕШМ дозволяє прогнозувати необхідність використання деяких груп допоміжних речовин для розробки складу та технології капсул з його вмістом, а саме: антифрикційних речовин для покращення плинності, розпушувальних речовин для покращення розпаду капсул, а також речовин, що сприяють ущільненню насипної маси, та вологорегулювальних речовин.

Ключові слова: *Salvia sclarea L.; шавлія мускатна; сухий екстракт; діуретична активність; фармакотехнологічні властивості; технологія твердих лікарських форм; тверді желатинові капсули*

Introduction. The genus *Salvia* L. is rich in species and accounts for about 700 species. Representatives of this genus are found both in wild and cultivated form [1-3]. Among the cultivated plants, *Salvia officinalis* L. and *Salvia sclarea* L. are used in medical practice, medicines containing them have anti-inflammatory, antibacterial, wound-healing, antioxidant, and analgesic effects. A wide range of pharmacological activity of *Salvia* L. representatives is due to a complex of biologically active substances, including triterpenoids, flavonoids, hydroxycinnamic acids, tannins [4-17]. Of great practical importance for the healthcare system is the use of the resources of the wild flora of the Republic of Tajikistan and, at the same time, sufficiently studied representatives for the development of medicinal products. From this point of view, in our opinion, the use of *Salvia sclarea* L. is promising. Expansion of the spectrum of the therapeutic use of *Salvia sclarea* L. plant and the development of a capsule dosage form containing a dry extract of clary sage is very relevant [18].

The Department of Pharmaceutical Technology and Pharmacology of the Tajik National University is developing hard gelatin capsules containing a dry extract of clary sage.

In the development of drugs in the form of hard gelatin capsules, including from the medicinal plant raw material, the study of the pharmacotechnological properties of the active substance and the substantiation of the encapsulation technology are of great importance. This is due to the fact that the pharmacokinetic characteristics of a medicinal product depend not only on its chemical compounds and the specific activity, but also on the physicochemical properties of the active substances, the composition and properties of excipients and the technology.

Therefore, the **aim** of the work was to study the pharmacological diuretic activity and pharmacotechnological properties of a dry extract of clary sage growing in Tajikistan.

Materials and methods. For the studies, we used DECS obtained at the Department of Pharmaceutical Technology and Pharmacology of the Tajik National University and standardized by the content of the total amount of flavonoids and hydroxycinnamic acids. The quantitative content of the total amount of flavonoids was not less than 13.0 % calculated with reference to apigenin, and the quantitative content of the total amount of hydroxycinnamic acids was not less than 1.2 % calculated with reference to rosmarinic acid. DECS was obtained by extraction with 70 % ethanol.

The pharmacotechnological properties of DECS were studied according to such methods of the State Pharmacopoeia of Ukraine (SPhU) as 2.9.12. Sieve analysis, 2.9.16. Fluidity, 2.9.34. Bulk density and tapped density, 2.9.36. Powder fluidity, 2.9.37. Optical microscopy, 2.2.32. Loss on drying [19].

The study of the diuretic activity of DECS was carried out at the premises of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy. The research was performed on white outbred female rats weighing 200 ± 20 g. The animals were kept in a separate room with controlled microclimate parameters [20]. The animals were on a balanced diet (granulated feed TU.U15.7-2123600159-001:2007) with free access to food and water (except for those stages of the study where this was due to the method). Animal care was performed following standard operations of the laboratory, all stages of the study were carried out according to the Directive 2010/63/EU of the European Parliament and the EU Council dated September 22, 2010 on the protection of animals used for scientific purposes [22].

Before the start of the experiment, the animals underwent acclimatization for 14 days. During the acclimatization period, each animal was daily examined (the behavior and general physiological state were assessed), the animals were observed to identify possible cases of morbidity or mortality. Before studying the diuretic activity, each rat was placed for 3 hours in a metabolic cage for acclimatization [20, 22].

Each stage of the study was reproduced according to the following design: 24 animals were divided equally into 4 experimental groups:

- negative control (NC);
- animals taking DECS in the dose of 100 mg/kg;
- animals taking DECS in the dose of 200 mg/kg;
- animals taking DECS in the dose of 300 mg/kg.

Before conducting experimental tests, the animals were given a suspension of the test substance in purified water daily on an empty stomach for 5 days. The C group animals received an adequate amount of the solvent. On day 5, permissive tests were performed on each animal cluster relative to the last administration.

The screening of the diuretic activity was performed with a rehydration load [23, 24]. Rats were deprived of free access to water overnight, after which they were intragastrically injected with saline in a volume of 25 mL/kg. Immediately after rehydration, the animal's bladder was emptied by pelvic pressure with tail pulling. In 45 minutes, test samples of DECS were administered in appropriate doses dissolved in purified water, so as to introduce an additional 6 mL/kg of liquid. After that, the animal was immediately placed in a metabolic cage. The volume of the excreted urine was collected and measured 5 hours after the administration of the test samples [23-25].

The results obtained were processed by descriptive statistics tools with an assessment of the normality of the distribution expressed as an arithmetic mean (M) and standard error of the mean (SEM). The experimental groups were compared using parametric analysis methods (ANOVA, Tukey HSD test). The significance of the differences was determined by the level of significance $P<0.05$. The statistical processing was carried out using the MS Excel 2007 and IBM SPSS Statistics 22 basic software package [26].

Results and discussion. Under the conditions of screening for the diuretic activity, all DECS doses tested a showed moderate diuretic activity. Thus, when using DECS in the dose of 100 mg/kg, the relative volume of urine excreted by rats for 5 hours increased by 1.9 times, in the dose of 200 mg/kg – by 2.0 times, in the dose of 300 mg/kg – by 1.8 times compared to the same indicator in the negative control group ($p<0.05$). It should be noted that there was no statistically significant difference in the diuretic activity of different doses of DECS, and no dose-dependent effect was observed. Taking into account the moderate severity of the effect, it is likely that the absence of a linear relationship was associated either with the achievement of a pharmacological plateau effect at the threshold of the dose of 100 mg/kg, or with the need to double the doses by higher orders of magnitude to register the dose-response relationship.

Taking into account the results of the study of the diuretic activity and scientific literature data on the spectrum of the pharmacological activity of *Salvia sclarea* L, given above, it is rational to consider DECS as a potential combined agent for use in nephrology.

To develop the composition and technology of hard gelatin capsules containing DECS, the studies of the pharmacotechnological properties of this substance were conducted. They are of key importance in the technology of solid dosage forms, and their value affects the choice of the necessary excipients.

The choice of the optimal production technology for capsules largely depends on the shape, surface nature, and linear dimensions of the active pharmaceutical substance. The physical and mechanical properties of powdered materials, including dry extracts, are due to their crystallographic structure, and, in turn, determine some technological characteristics, such as bulk density and compaction ability.

Table 1

A relative volume of the urine excreted in rats in 5 hours against the DECS background, n = 6, (M ± SEM)

Experimental Group	Diuresis, mL/100 g
Negative Control	0.57 ± 0.05
DECS, 100 mg/kg	1.07 ± 0.07*
DECS, 200 mg/kg	1.14 ± 0.09*
DECS, 300 mg/kg	1.02 ± 0.07*

Note: * – differences are significant in relation to the negative control ($p<0.05$).

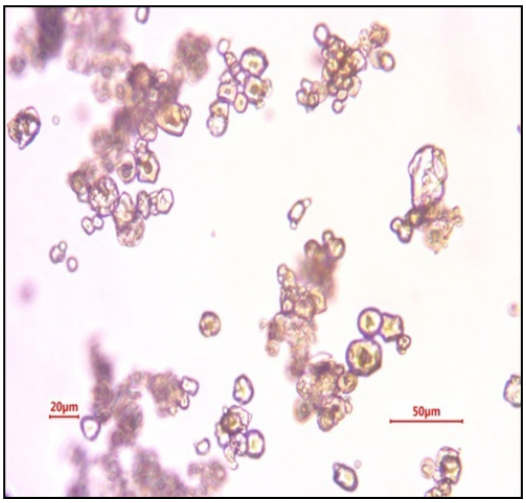
The shape and size of DECS particles was studied using a Lumam-P1 microscope. The results show that DECS is a fine amorphous powder with isodiametric particles and their fragments. The surface of the particles is slightly rough. Linear dimensions are from 5 to 50 μm (Fig. 1).

Based on the results of the crystallographic studies, some technological properties of DECS can be predicted. Thus, the insignificant particle size and its amorphous structure indicate the ability to form a bulk powder having a large bulk volume. And the roughness of the surface in combination with the dense stacking of particles contributes to the probability of their adhesion and, as a result, to a decrease in fluidity.

Dry extracts are usually hygroscopic, which is a critical parameter in the manufacturing process of capsules. Based on this, the hygroscopic properties of DECS at different relative humidity were studied [27].

Hygroscopicity was assessed by the method of determining the loss on drying after keeping the DECS weighing cup in a desiccator with a relative humidity of 100 %, 75 %, and 40 % at a temperature of 22 ± 2 °C.

The DECS description



The DECS micrograph

Fig. 1. DECS photos

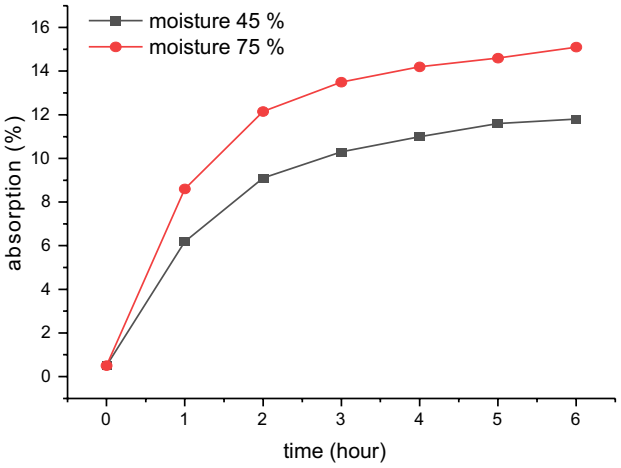


Fig. 2. The DECS moisture absorption with the relative humidity of 75 % and 40 %

The relative humidity of the air was created by water and saturated solutions of sodium chloride and sodium bicarbonate, respectively. Humidity was monitored by an Assman psychrometer, and the moisture content was determined by a Sartorius MA-150 express moisture analyzer. Initially, before the start of the experiment, DECS was kept in an oven for 24 hours at 45 °C. The results are presented in Fig. 2.

It was found that the most intensive moisture absorption was observed during the first hour of the experiment, reaching 6.18 % and 8.6 % with the air humidity of 40 % and 75 %, respectively. During the second hour, a fairly high moisture absorption was also observed, which gradually stabilized over the next 5 hours of the experiment, reaching 11.8 % and 15.1 %.

In the process of keeping DECS substance at 100 % humidity, 2 hours after the start of the experiment, the weight of the sample doubled, and in 8 hours the extract dissolved.

Significant hygroscopic properties of DECS substance indicate the risk of keeping wet mass formation during storage and make it possible to predict the choice of production conditions, as well as some excipients, namely hygroscopicity stabilizers.

The bulk weight, fluidity, compaction rate, and compaction factor of DECS most fully reflect its behavior when filling capsules and determine the possibility of using a direct encapsulation technology. Fluidity, bulk volume and tapped density of DECS were determined according to the SPhU on a GTB, "ERWEKA" vibration device for taking characteristics of bulk materials, and a SVM, "ERWEKA" device for vibration compaction of powders. The results are given in Tab. 2.

The bulk density quantitatively characterizes the ability of the powder to fill a unit volume (capsule body) and depends on the specific weight, dispersion, shape, and nature of the powder particles. Based on the data obtained, presented in Table 2, DECS had an average bulk density of 0.515 ± 0.002 g/mL. The quantitative assessment of fluidity showed that DECS had a very poor flowability, which value in the vibration mode of the device was 2.8 ± 0.1 g/s [27]. The angle of repose is an indirect characteristic of fluidity and was 52 °.

An equally important technological parameter affecting the quality of capsules is the fractional composition of DECS. The fractional composition of DECS was determined by the sieve analysis using a standard set of sieves following the SPhU requirements [19].

Table 2

Pharmacotechnological properties of DECS

Indicators	Units of measurement	Value
Description		A dry fine powder, brownish-green in color, with a characteristic odor and bitter taste
Flowability (d = 25 mm) – in vibration mode – no vibration	g/s	 2.8 ± 0.1 none
Bulk density	$m/_{V0}$	0.515 ± 0.002
Tapped density	m/V_{10}	0.629 ± 0.003
Tapped density	m/V_{500}	0.708 ± 0.002
Tapped density	m/V_{1250}	0.755 ± 0.003
Carr coefficient	%	31.79
Hausner ratio		1.47
Angle of repose	degree	52 ± 0.2
Fractional composition Particles greater than 7 mm Particles 0.5 to 7 mm Particles 0.355 to 0.5 mm Particles 0.25 to 0.355 mm Particles 0.18 to 0.25 mm Particles 0.09 to 0.18 mm Particles less than 0.09 mm	%	 – 0.9 ± 0.1 0.6 ± 0.1 1.8 ± 0.1 31.53 ± 0.05 53.15 ± 0.05 12.01 ± 0.04
Particle Shape		Isodiametric amorphous particles and their aggregates
Moisture content	%	5.94 ± 0.05

Based on the data obtained, which are presented in Table 2, it can be seen that the fraction of -0.19+0.09 mm is 53.15 %, the fraction of -0.25+0.19 mm is 31.53 %, and the fraction of -0.09 mm is 12.01 %.

According to the fractional composition, DECS has a clearly expressed fine fraction with a particle size of less than 0.25-0.09 mm 84.68 %. Such a fractional composition of the substance once again confirms the sufficiently low fluidity of the powder, which in practice can lead to uneven filling of the capsule. The positive point is that the main fraction is about 80 %, which will ensure the uniformity of the extract distribution in the capsule mass.

Conclusions and prospects for further research. The pharmacological studies indicate the presence of a moderate diuretic activity of DECS in the doses under study, which allows it to be considered as a potential medicinal product for use in nephrology or other pathological conditions accompanied by swelling of the body. The study of the pharmacotechnological indicators of DECS allows predicting the need to use certain groups of excipients to develop the composition and technology of capsules with its content, namely antifriction substances to improve flowability and disintegrants to improve capsule disintegration, as well as substances that contribute to the compaction of bulk mass and moisture-regulating agents. The balanced use of excipients of these groups will significantly improve the pharmacotechnological properties of DECS and allow for the application of a direct encapsulation technology.

Conflict of interests: authors have no conflict of interests to declare.

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